DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

June 26, 2000

Our Reference Number: 98-0656

Ms. Carol Moore
Bayer Corporation
800 Dwight Way
P.O. Box 1986
Berkeley, CA 94701-1986

Dear Ms. Moore:

Your submission to supplement your biologics license application for Antihemophilic Factor (Recombinant) to include a new formulation of the product, [Kogenate FS], and manufacture in a new facility, Building 60, has been approved.

We also acknowledge the following:

1. Your May 22, 2000 commitment to introduce the capping assay as an additional tool to determine the relative amount of terminal galactose on the Kogenate FS molecule. The assay will be performed on the intermediate UF-concentrate step prior to formulation. The initial action level will be a minimum of ———. Final container lots derived from intermediate lots exceeding this action level will not be dispositioned for release.

2. Your May 22, 2000 commitment to extend the existing qualitiative oligosaccharide pattern analysis to include quantitative action levels for highly branched N-linked oligosaccharide (HBNLO) peaks F and G on the intermediate UF-concentrate step prior to formulation:

   Peak F ratio: min. — max. —
   Peak G ratio: min — max. —

   Final container lots derived from intermediate lots exceeding these actions levels will not be dispositioned for release.

3. Your May 23, 2000 commitment to initiate the validation of bulk hold for Kogenate FS in ——— with the expectation of completion of the report, including interim stability by ——— The validation requires —— commercial-scale lots that will be purposely held up to ——— as a liquid bulk and encompass the time through the sterile fill. Once lyophilized, the lots will be placed in the stability program to evaluate any impact that the liquid-state hold may have on the overall product stability. Until the completion of the validation

and concurrence by CBER, final container lots that exceed the currently supported ——— hold time will not be dispositioned for release.

4. Your May 31, 2000 commitment to complete the ongoing clinical trial to assess the pharmacokinetics of Kogenate FS with high levels of HBNLO under ——— ——————— and to submit a final report on this study within one year of the date of this letter.

5. Your July 15, 1999 and April 19, 2000 commitments to reassess in-process alert and action limits and product release specifications after — lots have been manufactured.

6. Your April 19, 2000 commitment to develop release assays for the ——— ——————— , consisting of total protein and quantitative ——— analysis, by the end of ——— .

7. Your April 19, 2000 commitment to report on your evaluation of implementing additional in-process control testing for LAL by ———

This information has been placed in your biologics license file. It is recommended that a copy of this letter be available for review at the time of FDA inspections

Sincerely yours,

For Jay S. Epstein, M.D.
Director
Office of Blood Research and Review
Center for Biologics
Evaluation and Research